REMARKS

The Examiner's continued attention to the present application is noted with appreciation.

Submitted herewith is the "Sequence Listing" identifiers amendment to the disclosure, wherein reference is made to the sequence by use of assigned identifier (37 CFR 1.821(d)); a substitute "Sequence Listing" computer readable form copy and substitute paper copy (37 CFR 1.821(e) and 1.824); and the required statement that the paper and computer readable copies are the same and include no new matter (37 CFR 1.821(g).

In view of the above amendments and remarks, it is respectfully submitted that all grounds of objection to nucleotide sequence and/or amino acid sequence disclosures have been addressed. It is believed that the case is now in condition for examination and same is respectfully requested.

Attached hereto is a marked-up version of the changes made to the specification by the current amendment. The attached paper is captioned "**Version with Markings to Show Changes Made**."

Authorization is given to charge payment of any additional fees required, or credit any overpayment, to Deposit Acct. 13-4213.

Respectfully submitted,

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"Version with Markings to Show Changes Made"

In the disclosure (page 5, line 9):

Peptides containing the adhesive sequence RGD are under active investigation as anti-thrombotic agents (Imura Y, Stassen J-M, Dunting S, Stockmans F, and Collen D: Antithrombotic properties of L-cysteine, N-(mercaptoacetyl)-D-Tyr-Arg-Gly-Asp-sulfoxide (G4120) in hamster platelet-rich femoral vein thrombosis model, *Blood* 80:1247-1253, 1992). Knight et al. (Knight LC, Radcliffe R, Maurer AH, Rodwell JD and Alvarez VL: Thrombus imaging with Tc-99m synthetic peptides based upon the binding domain of a monoclonal antibody to activated platelets. *J Nucl Med* 35:282-288, 1994) have reported on the use of ^{99m}Tc-synthetic peptide-metallothionein complexes, containing the radiometal binding sequence Lys-Cys-Thr-Cys-Cys-Ala, <SEQ ID NO:6> which bind to the platelet glycoprotein IIb/IIIa complex to image fresh thrombi in jugular and femoral veins. Other RGD-containing sequences are disclosed in U.S. Patent No. 5,395,609, *Synthetic Peptides for Use in Tumor Detection*, to Stuttle AWJ.

In the disclosure (page 5, line 16-17):

Radiolabeled peptide constructs, with two binding sequences coupled to DTPA, have been reported. A dimer ^{111}In-DTPA-labeled laminin sequence was prepared for tumor imaging, in which the dimer was formed by reacting a peptide sequence containing a single YIGSR <SEQ ID NO:7>with DTPA dianhydride, yielding a dimer represented by the formula DTPA-(GYIGSR-NH_2)$_2$ <SEQ ID NO:8>. In preliminary studies the dimer was more potent than a peptide with a single YIGSR sequence. Swanson D, Epperly M, Brown ML et al: In-111 laminin peptide fragments for malignant tumor detection. *J Nucl Med* 34:231P, 1993 (Abstract). A dimer of a melanotropin analogue linked to ^{111}In-DTPA in a similar fashion has also been reported as an imaging agent for metastatic melanoma. Wraight EP, Bard DR, Maughan TS et al, *Br J Radiology* 65:112-118, 1992; and Bard DR, Wraight EP, Knight CG: BisMSH-DTPA: a potential imaging agent for malignant melanoma. *Ann NY Acad Sci* 680:451-453, 1993.

In the disclosure (page 21, line 6):

It is also possible to construct peptides with a conformationally constrained biological-function domain specific for receptors to the tripeptide sequence Arg-Gly-Asp, but not necessarily of the general formulas given above, such as:

D-Arg-Gly-D-Cys,

Arg-Gly-D-Cys,

HOOC-$(CH_2)_2$-CO-Phe-Gly-Cys-Arg, <SEQ ID NO:9>

HOOC-$(CH_2)_4$-CO-Gly-Lys-Cys, and

HOOC-$(CH_2)_5$-CO-Gly-Lys-Cys.

In the Disclosure (page 42, line 29):

Metal-Peptide Backbone. A variety of metal ion-complexing backbones may be utilized in this invention. The selection of backbone depends, in large part, on the metal ion to be employed, the biological receptor and the size and characteristics of the biological-function domain required for the biological receptor. The preferred metal-peptide backbone is based on the requisite number of particular coordinating groups required by the coordination sphere of a given complexing metal ion. In general, most of the metal ions that may prove useful in this invention have a coordination number of four to six, and rarely as high as eight, which implies that the putative metal ion-binding peptide chain must have sufficient groups placed in the peptide chain in a stereocompatible manner so as to establish a bond with a metal ion of given geometry and coordination sphere. Coordinating groups in the peptide chain include nitrogen atoms of amine, amide, imidazole, or guanidino functionalities; sulfur atoms of thiols or disulfides; and oxygen atoms of hydroxy, phenolic, carbonyl, or carboxyl functionalities. In addition, the peptide chain or individual amino acids can be chemically altered to include a coordinating group, such as oxime, hydrazino, sulfhydryl, phosphate, cyano, pyridino, piperidino, or morpholino groups. The peptide construct can be either linear or cyclic; however, the linear construct is generally preferred. One example of a small linear peptide is Gly-Gly-Gly-Gly, <SEQ ID NO:10> which has four nitrogens (an N_4 complexation system) in the backbone that can complex to a metal ion with a coordination number of four. Any similar suitable tetrapeptide could be so employed; in addition, a tripeptide in which at least one of the amino acids has a side chain with a coordinating group can be employed with a metal ion with a coordination number of four. The side chain can have a nitrogen, oxygen or sulfur-based coordination group. Thus, a tetradentate peptide construct could be N_4, N_3S, N_2S_2, NS_3, N_2SO or any similar combination yielding tetradentate coordination utilizing nitrogen, sulfur and oxygen atoms. Cyclic sequences may be employed; for example, cyclo[Gly-Gly-Gly-Gly] is a

simple cyclic peptide which yields an N_4 tetradendate ligand suitable for complexing a metal ion with a coordination number of four. Other suitable modifications to this cyclic tetrapeptide template can be structurally engineered in a manner similar to that described above for a linear peptide to convert it to any of the other tetradendate ligand systems described above.

In the disclosure (page 53, line 14):

The products of this invention, and products made by the methods of this invention, may be used for any radiopharmaceutical application for which a biologically active peptide or protein molecule may be employed. This includes, but is not limited to, products which are based on the binding site of antibody fragments, including F(ab□)$_2$, Fab, Fv and Fc fragments of monoclonal antibodies, or are otherwise based on the hypervariable region of monoclonal antibodies, including single-chain binding proteins. This also includes other antigen binding domain fragments and biologically active peptides. This allows the rational development of peptide-based imaging and therapeutic agents, by using the methods of this invention, to design and make a peptide, including a peptidomimetic or psuedopeptide, which upon labeling with a metal ion mimics the known binding characteristics of the parent molecule. Examples of suitable products which may be made by the methods of this invention include peptides which have biological-function domains, upon labeling with a metal ion, functionally similar to those of RGD, YIGSR <SEQ ID NO:7>, For-MLF, TGF-beta (tumor growth factor), FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), EGF (epidermal growth factor), NGF (nerve growth factor), neuropeptide Y, cholecytokinin, tumor-related markers, hormones such as estrogen, tuftsin, melanotropin, somatostatin and the like. Over 300 receptors and their agonists are known, each of which is a potential candidate for a product of this invention.

In the Disclosure (page 70, line 8):

To construct a conformationally constrained peptide using the method of this invention, a peptide molecular construct to bind a technetium (or rhenium) metal ion, with the ability after binding the metal ion to bind a platelet fibrinonectin receptor, was designed so that the four available valences of the core of reduced technetium (or rhenium) oxide [V] were coordinated to a peptide sequence capable of complexing the metal. A tripeptide sequence providing an N_3S_1 metal ion-complexing backbone, which specifically binds a technetium or rhenium metal ion, was utilized as the starting material. To mimic the biological binding of the RGD sequence, it was determined that the two most important and primary structural aspects required for making receptor contact to the GP IIb/IIIa complex are a positively charged side chain and a negatively charged side chain analogous to the side chains of Arg and Asp residues in typical fibrinonectin peptides containing the receptor active sequence Arg-Gly-Asp (RGD sequence). Decorating the metal-peptide scaffold with these two side chains yielded the RGD mimic tetrapeptide Arg-Gly-Cys-β-Ala, <SEQ ID NO:1> which is a putative candidate for the platelet fibrinonectin receptor. Further refinements in the structure were made in response to other considerations, including stereochemistry of the side chains of the optically active amino acids, higher *in vivo* stability of the resulting peptide, higher blood residence time *in vivo*, and the ease of complexing with the metal ion in the desired configuration. Based on these considerations, a peptide of the following general formula was designed:

In the Disclosure (page 72, line 16 and 22 - page 73, line 1):

A number of metallopeptide constructs were synthesized as mimics of the RGD sequence for various integrin receptors, such as the α_{IIb}-β_3, α_v-β_3, and α_5-β_1 receptors. These constructs were synthesized to bind either ^{99m}Tc or ReO[V]. The following constructs were synthesized, shown with an Re label (the presumptive metal ion-binding domain is shown in brackets):

ReO[V]-[Arg-Gly-Cys]-β-Ala <SEQ ID NO:1>

ReO[V]-[D-Arg-Gly-Cys]-β-Ala

ReO[V]-[Arg-Gly-D-Cys]-β-Ala

ReO[V]-[D-Arg-Gly-D-Cys]-β-Ala

ReO[V]-[D-Lys-Gly-Cys]-β-Ala

ReO[V]-[D-Lys-Gly-Cys]-Gly

ReO[V]-[Gly-Arg-Cys]-β-Ala <SEQ ID NO:2>

ReO[V]-[Gly-D-Arg-Cys]-β-Ala

ReO[V]-[Gly-Arg-D-Cys]-β-Ala

ReO[V]-[Gly-D-Arg-D-Cys]-β-Ala

ReO[V]-[D-Arg-D-Phe-D-Cys]-β-Ala

ReO[V]-[D-Arg-Gly-D-Cys]

ReO[V]-[Arg-Gly-D-Cys]

ReO[V]-C_6H_5-CH_2-CO-[D-Arg-Gly-D-Cys]-β-Ala

ReO[V]-[Phe-Arg-D-Cys]-β-Ala

ReO[V]-HOOC-$(CH_2)_2$-CO-[Phe-Gly-Cys]-Arg <SEQ ID NO:9>

ReO[V]-HOOC-$(CH_2)_4$-CO-[Gly-Lys-Cys]

ReO[V]-HOOC-$(CH_2)_5$-CO-[Gly-Lys-Cys]

In the Disclosure (page 108, line 19 and line 26):

^{99m}Tc-Labeled Construct	**Routes of Adminis-tration**	**Time Point (Min.)**	**% Peak Bound of Labeled Construct**	**% Peak Bound in Urine**
^{99m}Tc-[Arg-Gly-Cys]-β-Ala <SEQ ID NO:1>	iv	30-120	100%	100%
^{99m}Tc-[D-Arg-Gly-D-Cys]-β-Ala,	iv, sc	30-120	100%	100%
^{99m}Tc-[Arg-Gly-D-Cys]-β-Ala	iv	30-120	100%	100%
^{99m}Tc-[D-Arg-Gly-Cys]-β-Ala	iv	30-120	100%	100%
^{99m}Tc-[Gly-Arg-D-Cys]-β-Ala	iv	30-120	100%	100%
^{99m}Tc-[Gly-D-Arg-D-Cys]-β-Ala	iv	30-120	100%	100%
^{99m}Tc-[Gly-D-Arg-Cys]-β-Ala	iv	30-120	100%	100%
^{99m}Tc-[Gly-Arg-Cys]-β-Ala <SEQ ID NO:2>	iv	30-120	100%	100%
Thr-^{99m}Tc-[D-Lys-Gly-D-Cys]-Arg	iv, sc, oral	30-120	100%	100%
Tyr-^{99m}Tc-[Gly-Phe-NH-$(CH_2)_2$SH]	iv	30-120	100%	100%

In the Disclosure (page 115, line 7):

Platelets contain a 67 kDa receptor which binds to laminin-derived peptide sequences containing Tyr-Ile-Gly-Ser-Arg (YIGSR) <SEQ ID NO:7> (Tandon NN, Holland EA, Kralisz U, Kleinman HK, Robey FA, and Jamieson GA: Interaction of human platelets with laminin and identification of the 67 kDa laminin receptor on platelets. *Biochem J* 274:535-542, 1991). This platelet receptor appears to play an important role in the interaction of platelets with the intact laminin molecule. Platelet adherence to laminin via this receptor does not in itself result in platelet activation (Ill CR, Engvall E, and Ruoslahti E: Adhesion of platelets to laminin in the absence of activation. *J Cell Biol* 99:2140-2145, 1984).